REMARKS

Claims 89-98 and 100-127 are pending in the application. Claims 89 and 90 have been amended to recite an in vitro composition of cells comprising modified cells of an inbred strain of an animal and one or more of: (i) unmodified cells of an inbred strain of an animal; (ii) the progenies of the modified cells; and (iii) the progenies of the unmodified cells. Claim 89 has also been recited that the composition is being produced by a method comprising introducing a targeting DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro. The amendment is fully supported by the originally filed specification and claims. In particular, support for the amendments can be found, *inter alia*, at page 28, lines 30-37; page 35, lines 20-21 in the specification.

No new matter has been added. Entry of the amendments and the following remarks to the file are respectfully requested.

I. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, IS OBVIATED

Claims 89-98, and 100-127 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner states that the phrase "modified cells and unmodified cells . . ., and/or the progenies thereof" is vague. Applicants respectfully disagree. However, in order to expedite prosecution, claims 89 and 90 have been amended to recite that the composition comprises modified cells of an inbred strain of an animal and one or more of: (i) unmodified cells of an inbred strain of an animal; (ii) progenies of the modified cells; and (iii) progenies of the unmodified cells. Applicants submit that claims 89-98, and 100-127 in the present invention clearly apprises one of ordinary skill in the art of its scope and are definite.

II. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, IS OBVIATED

Claims 89-98 and 100-127 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification, while being enabling for isolated modified cells and unmodified cells of an inbred strain of an animal, does not reasonably provide enablement for a composition, which is an organ or tissue, comprising said modified and unmodified cells. The Examiner alleges that the claimed composition can read on an organ or a tissue. Applicants respectfully disagree with the contention that the full scope of the claim is not

enabled. However, in order to expedite prosecution, and without admitting that the specification does not enable a composition that is an organ or tissue, claim 89 has been amended to recite "an in vitro composition of cultured cells". As such, the claim particularly points out and distinctly claims a composition of cells that are isolated in culture and does not read on an organ or a tissue. This rejection is thus obviated.

The Examiner further alleges that the claims read on introducing a targeting DNA construct into a plurality of any unmodified cells so as to provide a composition comprising modified calls and unmodified cells of an inbred strain of an animal. The Examiner alleges that according to the recitation of the present claim, the unmodified cells need not be isolated from an inbred strain of an animal. In response, claim 89 has been amended to recite that the *in vitro* composition of cultured cells is produced by a method comprising introducing a targeting DNA construct into a plurality of unmodified cells of an inbred strain of animal *in vitro*. With the amendment, it is required that unmodified cells of an inbred strain of animal be used in the method. Amended claim 89 does not read on introducing a targeting DNA construct into a plurality of any unmodified cells.

In view of the foregoing amendments, Applicants submit that the specification reasonably provides enablement for claims 89-98, and 100-127 in the present invention. Applicants request that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

III. CLAIM REJECTIONS UNDER 35 U.S.C. § 102

A. The Rejection under 35 U.S.C. § 102(b) Is In Error

Claims 89-98, 100-127 have been rejected under 35 U.S.C.§ 102(b) as being anticipated by Capecchi, 1989, Trends in Genetics, 5(3):70-76 ("Capecchi"). Applicants submit that the rejection is in error.

The Examiner states that Capecchi teaches "[t]hrough gene targeting, the potential now exists to generate mice of any desired genotype. The experimenter chooses both which gene to mutate and how to mutate it. The criteria for selecting which gene to mutate can be based on knowledge generated within the species or from other species." The Examiner further states that "Capecchi also teaches using available cloned mouse genes or genomic fragment of the mouse genes for gene targeting via homologous recombination." The Examiner alleges that these teachings anticipate the present invention because "it is inherent that one of ordinary skill in the art would use the flanking sequences of the targeting DNA construct derived from the

same inbred strain of animal as the targeted cells." (Page 5 of the Office Action). Applicants submit that these teachings of Capecchi does not support the Examiner's contention that Capecchi anticipates the present invention inherently or otherwise.

The Examiner has not provided a sound basis in fact and/or technical reasoning to support the allegation that the use of a single inbred strain of animal as the sources of both the flanking sequences of the targeting DNA construct and the targeted cells would necessarily flow from the teachings of Capecchi and that such use in the teachings would be recognized by one of ordinary skill in the art. Capecchi's statement that the "experimenter chooses both which gene to mutate and how to mutate" says nothing about the genomic DNA flanking the gene that is to be mutated. Similarly, Capecchi's reference to "knowledge generated within the species or from other species" only applies to selecting which target gene to mutate. It is silent as to the genetic background of the animal from which the target gene originates. Accordingly, it cannot be said that the use of a single inbred strain of animal as the source of both the flanking sequences of the targeting DNA construct and the targeted cells is disclosed in the teachings of Capecchi. Applicants submit that Capecchi does not anticipate the claimed invention.

At best, Capecchi merely indicates that one can use any available cloned mouse genes or any available genomic fragment of the mouse genes for gene targeting via homologous recombination (page 70, right column, 2nd paragraph, in Capecchi). The statements in Capecchi quoted by the Examiner do not concern the genetic background of the genome of the embryonic stem cell. As indicated in a Declaration of the inventor, Dr. Anton Berns, dated March 14, 1995 ("Berns Declaration"), submitted for the parent U.S. patent application, Serial No. 08/216,121 (a copy of which is enclosed herewith as Exhibit 1), research in gene targeting was mostly carried out using ES cells from the 129 strain of mouse. However, at the time of the invention, most of the mouse genome libraries used for making the targeting DNA construct were derived from the BALB/c or Black 6 mouse strains (see paragraph 12). Genomic library from mouse strain 129 was not available to the public. Evidently, as shown in paragraph 13, there were numerous requests for the mouse strain 129 genomic library, which Dr. Berns constructed. Thus, without the teachings of the present invention of using the same inbred strain of animal as the source of both flanking sequences and targeted cells, a scientist intending to target a particular gene would use a clone that was easily available instead of going to the considerable time, effort and expense of obtaining flanking sequences of the targeting DNA construct from the same inbred strain of animal as the targeted cells. There is

no teaching anywhere in Capacchi that the source of the targeting mutant DNA and its flanking sequences and the targeted ES cells must be derived from the same inbred strain of animal. Applicants submit that, Capecchi does not teach that the flanking sequences and the targeted ES cells have to match by having the same genetic background. Accordingly, the missing descriptive matter, *i.e.*, the use of the same inbred strain of animal as the source of both flanking sequences and targeted cells to perform homologous recombination, would not be recognized by persons of ordinary skill as being necessarily present in the general teachings of Capecchi.

According to applicable case law, to rely upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993).

For the teaching in Capecchi to rise to the level of inherent anticipation, it is not enough that it is possible that the flanking sequences of the target gene and the targeted cells may be derived from the same inbred strain of mice. The mere fact that the sequences flanking the target gene and the targeted cells may be derived from the same inbred strain of animal, without being an inevitable result, does not support inherent anticipation. Applicants submit that Capecchi does not inherently anticipate the present invention.

Accordingly, Applicants request that the rejection of claims 89-98, 100-127 under 35 U.S.C.§ 102(b) as being anticipated by Capecchi be withdrawn.

B. The Rejection under 35 U.S.C. § 102(b) Is In Error

Claims 89-98 and 100-127 have been rejected as being anticipated by U.S. Patent 5,464,764 issued to Capecchi et al. (" the '764 Patent"). Applicants point out that the '764 Patent is not a reference under 35 U.S.C. § 102(b) since the present application has a priority

date of August 20, 1991 and the '764 Patent issued on November 7, 1995. The rejection is in error and should be withdrawn.

To be fully responsive to the office action notwithstanding the error in the rejection, Applicants note that the Examiner states that the '764 patent teaches a method for producing an alteration in a gene of interest by targeting through homologous recombination using mouse embryonic stem cells (page 6, Office Action dated May 11, 2003; page 7 of Office Action dated August 22, 2006). However, the '764 patent relates to positive-negative selector (PNS) vectors which comprises, in addition to the mutated target gene and a region of substantial sequence homology that facilitates homolgous recombination, a third and a fourth sequence encoding respectively a positive selection marker and a negative selection marker (see column 5, lines 3-20). Applicants submit that the '764 patent fails to disclose each and every element of independent claim 89 and its dependent claims 90-98 and 100-127. The present invention is not anticipated because the '764 patent does not teach the use of a single inbred strain of animal as the sources of both the flanking sequences of the targeting DNA construct and the targeted cells.

In an example provided in the '764 Patent (column 22, lines 53-54), the construction of the targeting DNA was carried out as described in Thomas and Capecchi, 1987 (Cell 51:503-512; "Thomas") (Reference C60 in Information Disclosure Statement submitted August 17, 2005) (Exhibit 2). In Thomas, the target DNA and flanking sequences of the targeting DNA construct were obtained from a gene library made from the genomic DNA of cells from the mouse ARK cell line. The targeted cells used in the '764 patent were derived from mouse line C57BL/6 or CC1.2 (col. 23, lines 40-63). Clearly, the flanking sequences of the targeting DNA construct and the targeted cells in the '764 patent were not derived from the same inbred animal as recited in the present claims. Therefore, the '764 patent does not teach the limitation that the targeting DNA construct and the targeted cells are derived from the same inbred animal.

In view of the foregoing, the '764 patent does not anticipate the present invention.

IV. REJECTION BASED ON NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 89-98, 100-127 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-23 of U.S. Patent No. 6,653,113 to Berns ("the '113 patent") and claims 1-18 of U.S. Patent No.

5,789,215 ("the '215 patent") to Berns. In response, while not admitting that the claims of the above-identified patent application are not patentably distinct from claims 1-23 of the '113 patent or claims 1-18 of the '215 patent, Applicants, upon indication of allowable subject matter, will submit a Terminal Disclaimer under 37 C.F.R. § 1.321(c) for the above-identified application.

CONCLUSION

Entry of the foregoing amendments and consideration of the foregoing remarks are respectfully requested. No fee is believed to be due for this amendment. Should any fee be required, please charge such fee to Jones Day Deposit Account No. 50-3013. Applicants respectfully submit that all claims are now in condition for allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining issues.

Respectfully submitted,

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